a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) choosing an oligonucleotide chemistry;

c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;

d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step b) and said oligonucleotide chemistry of step c);

e) robotically assaying said set of synthetic oligonucleotides of step d) for a physical, chemical or biological activity; and

f) selecting a subset of said set of oligonucleotides of step d) having a desired level of physical, chemical or biological activity.

99. (Twice Amended) A method comprising:

evaluating *in silico* a plurality of virtual compounds according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically synthesizing a plurality of synthetic compounds corresponding to said plurality of virtual compounds.

REMARKS

Claims 55, 56, 58-72, 74-87 and 99-102 are pending in the present application. Claims 55, 56, 58, 59, 72, 74, 75, 78-82, 86, 87, and 99 have been amended herein, support for which can be found throughout the specification. Upon entry of the present Amendment, claims 55, 56, 58-72, 74-87, and 99-102 will remain pending.

I. The Claimed Inventions Are N t Obvious

Claims 55, 56, 58-72, 74-87, and 99-102 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over the combination of U.S. Patent No. 5,463,564 (hereinafter, the "Agrafiotis reference"), Uhlmann *et al.*, *Chem. Rev.*, **1990**, *90*, 543-584 (hereinafter, the "Uhlmann reference") and U.S. Patent No. 5,639,603 (hereinafter, the "Dower reference") taken further in view of U.S. Patent No. 5,720,923 (hereinafter, the "Haff reference") or U.S. Patent No. 5,650,122 (hereinafter, the "Harris reference"). The Office Action asserts that it would have been *prima facie* obvious for one skilled in the art to perform the desired compound design via the Agrafiotis and Uhlmann references and synthesize the compounds via the Dower reference and then perform the assays as desired using the Haff and/or Harris references. Applicants traverse the rejection and respectfully request reconsideration because the subject matter of claims 55, 56, 58-72, 74-87, and 99-102 is neither disclosed nor suggested by the collective teachings of the cited references.

The references cited in the Office Action do not teach or suggest all the elements of the rejected claims. To establish *prima facie* obviousness, the references relied upon must teach or suggest all the elements of the claimed subject matter. M.P.E.P. § 2143.03 (citing *In re Royka*, 180 U.S.P.Q. 580 (C.C.P.A. 1974)). For example, the claims recite "generating *in silico* virtual compounds," "evaluating *in silico* a plurality of virtual compounds," "generating a library of nucleobase sequences *in silico*," "evaluating *in silico* a plurality of virtual compounds," "evaluating *in silico* a plurality of virtual nucleotides" or similar language, "according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence." Contrary to the assertions in the Office Action, the Agrafioits reference does not include these steps.

The Office Action asserts that the Agrafiotis reference describes "computer controlled design of compounds and testing thereof." The Agrafiotis reference, however, simply uses a "directed diversity chemical library" to generate instructions for mixing chemical building blocks to create new compounds. *See* Col. 5, l. 23 through col. 6, l. 61. The actual compounds are then physically evaluated and the information is added to the "directed diversity chemical library" to form an iterative process by which the "directed diversity chemical library" is expanded. *See id.* The

"directed diversity chemical library" of the Agrafiotis reference begins with a set of chemical building blocks with known characteristics and its expansion is limited to an iterative process of synthesizing compounds from the set of chemical building blocks.

Applicants' claimed methodology begins with a target nucleic acid sequence and then generates virtual compounds *in silico* according to defined criteria. Unlike the Agrafiotis reference, Applicants' virtual compounds do not originate from an iterative process of synthesizing and analyzing compounds prepared from a set of chemical building blocks with known characteristics. Rather, the virtual compounds of Applicants' claimed invention originate from an analysis of the target nucleic acid sequence. Specifically, Applicants' claimed invention generates *in silico* virtual compounds according to defined criteria, including thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequences, or uniform distribution to target nucleic acid sequence. In contrast, the references cited in the Office Action do not teach or suggest all of the elements of Applicants' claimed invention. The Examiner is requested to particularly point out where the combination of cited references teaches these elements recited in the claims.

Not only must the elements of the claimed subject matter be taught or suggested by the prior art, to establish *prima facie* obviousness, there must be some reason or motivation for one skilled in the art to modify or combine the teachings of the prior art to produce the claimed invention. *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). The examiner has the burden of presenting factual evidence which would indicate that the claimed methods are *prima facie* obvious. *Id.*; M.P.E.P. § 2142. It is impermissible for an examiner, in proffering a 35 U.S.C. § 103 rejection, to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art to render the claimed invention obvious. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). "[T]he best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). The Federal Circuit recently summarized precedent concerning obviousness rejections and stated the "need for specificity pervades this authority." *In re Lee*, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002) (rejecting the Board's proposition that a "specific hint or suggestion" of motivation to combine was

not required). The Office Action fails to provide adequate support for its assertion that one skilled in the art would be motivated to modify or combine the teachings of the cited references to produce the claimed invention. Applicants respectfully traverse the Office Action's conclusory statement and request that the examiner point out the alleged motivation for combining the cited references.

In view of the foregoing, the claimed inventions are not obvious in view of the combination of the cited references. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

II. The Claims are Clear And Definite

Claims 55, 56, 58-61, 72, 74-87, and 99 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as their invention. Applicants respectfully request reconsideration in view of the amended claims.

Applicants first note that the Office Action has included claims 60 and 61 in the rejection. Claims 60 and 61 do not include preamble language in common with the remainder of the rejected claims. Rather, claims 60 and 61 begin "[a] method of generating a set of oligonucleotides comprising..." Claims 60 and 61 clearly include the step of generating compounds. Therefore, contrary to the Office Action's assertion, the metes and bounds of claims 60 and 61 are defined by steps within the body of the claim.

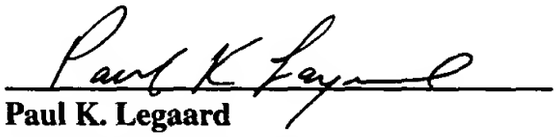
Although Applicants maintain that the remaining rejected claims are clear and definite as written, solely to advance prosecution of the present application, Applicants have amended claims 55, 56, 58, 59, 72, 74, 75, 78-82, 86, 87, and 99 to remove any reference to "defining" or "identifying" within the preamble.

In view of the foregoing, all claims are clear and definite. Persons of ordinary skill in the art would have no difficulty in determining what subject matter is within the scope of the claims. Accordingly, Applicants respectfully requests that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

III. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (215) 564-8906 if there are any questions regarding Applicants' claimed invention. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 55, 56, 58, 59, 72, 74, 75, 78-82, 86, 87, and 99 have been amended as follows:

55. (Twice Amended) A method [of defining a set of compounds] comprising:

generating *in silico* virtual compounds according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence, wherein said virtual compounds modulate the expression of a target nucleic acid sequence;

synthesizing compounds corresponding to at least some of said virtual compounds; and

robotically assaying said synthetic compounds for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

56. (Twice Amended) A method [of defining a set of compounds] comprising:

evaluating *in silico* a plurality of virtual compounds according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically assaying a plurality of synthetic compounds corresponding to at least some of said virtual compounds for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

58. (Twice Amended) A method [of defining a set of compounds] comprising:

generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically assaying a plurality of synthetic compounds having at least some of said nucleobase sequences for one or more desired physical, chemical or biological properties by

computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

59. (Twice Amended) A method [of defining a set of compounds] comprising:

evaluating *in silico* a plurality of virtual compounds according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically assaying a plurality of synthetic compounds corresponding to at least some of said virtual compounds for one or more desired physical, chemical or biological properties.

72. (Twice Amended) A method [of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences] comprising:

evaluating *in silico* a plurality of virtual oligonucleotides according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically assaying a plurality of synthetic oligonucleotides corresponding to least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

74. (Twice Amended) A method [of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences] comprising:

generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically assaying a plurality of synthetic oligonucleotides having said nucleobase sequences for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

75. (Twice Amended) A method [of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences] comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

78. (Twice Amended) A method [of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences] comprising:

a) evaluating *in silico* a plurality of virtual oligonucleotides according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

79. (Twice Amended) A method [of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences] comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to least some of said plurality of virtual oligonucleotides; and

d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

80. (Twice Amended) A method [of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences] comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) choosing an oligonucleotide chemistry;

c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;

d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step b) and said oligonucleotide chemistry of step c);

e) robotically assaying said set of synthetic oligonucleotides of step d) for a physical, chemical or biological activity; and

f) selecting a subset of said set of oligonucleotides of step d) having a desired level of physical, chemical or biological activity.

81. (Twice Amended) A method [of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences] comprising:

evaluating *in silico* a plurality of virtual oligonucleotides according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically assaying a plurality of synthetic oligonucleotides corresponding to least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties.

82. (Twice Amended) A method [of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences] comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties.

85. (Twice Amended) A method [of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences] comprising:

a) evaluating *in silico* a plurality of virtual oligonucleotides according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

86. (Twice Amended) A method [of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences] comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to least some of said plurality of virtual oligonucleotides; and

d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

87. (Twice Amended) A method [of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences] comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) choosing an oligonucleotide chemistry;

c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;

d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step b) and said oligonucleotide chemistry of step c);

e) robotically assaying said set of synthetic oligonucleotides of step d) for a physical, chemical or biological activity; and

f) selecting a subset of said set of oligonucleotides of step d) having a desired level of physical, chemical or biological activity.

99. (Twice Amended) A method [of defining a set of compounds] comprising:

evaluating *in silico* a plurality of virtual compounds according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically synthesizing a plurality of synthetic compounds corresponding to said plurality of virtual compounds.